UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM JUN 17 1980

OFFICE OF TOXIC SUBSTANCES

SUBJECT: EPA Reg.#10182-RO; 10182-EUP-11; Baquacil
CASWELL#676

FROM: William Dykstra
Toxicology Branch (TS-769)

WJD 6/9/80
WJB

TO: A.E. Castillo (12)
Registration Division (TS-767)

Recommendations:

1) The label signal word is Danger on the basis of eye irritation.

2) Re-evaluation of 26-week dog study review (memo of 6/15/78) with 20% PHMB indicates that 500 ppm (low dose) can be considered the NOEL for the study.

3) The conditional registration can be toxicologically supported.

4) For registration the following toxicity data are required:

   (A) Individual Draize scores on rabbit skin irritation study.

   (B) Historical data on soft and skeletal tissue anomalies from FDRL.

   (C) Nitrosamine Analytical reports on technical material.

5) The toxicity studies submitted are acceptable as either supplementary data or core-minimum data.

Review:

1) C-32. Skin Irritation in the Rabbit (Divisional ORG/13/79; CTL Y00156/002; D. Eaton; Report No. CTL/T/1362)

   Test Material: Vantocil P, pH 5.8

   0.5 ml of test material was applied to intact and abraded skin sites on the fur clipped trunk of six albino rabbits under an impervious cuff for 24 hours. Observation and scoring at 24, 48 and 72 hours after exposure.

   Results: P.I. = 2.6 at 72 hours

   Signs of small white scabs were seen on the intact and abraded skin sites up to 10 days following the application.

   Classification: Supplementary Data

(a) Draize scores not provided in report.

2) C-33. Acute Oral and Dermal Toxicity (Divisional ORG/13/79; CTL Y000156/002; S.J. Jackson; Report No. CTL/T/1361)

Test Material: Vantocil P, pH 5.8

Acute Oral Toxicity

Groups of 5 male and 5 female animals were fasted for 16-20 hours and then given doses of 700, 1000, 1500, 2000, 2500, 3000, 3500, 5000 mg/kg of an aqueous solution of Vantocil P. The solution was administered by stomach tube and the animals were observed for 14 days. A standard volume of 10 ml/kg was dosed to each animal, differences in dose level being acheived by altering the concentration of the dosed solution.

Results: LD50 (males) = 2747 mg/kg (2131-3549 mg/kg)

LD50 (females) = 2504 mg/kg (2025-2969 mg/kg)

Toxic Signs: Slight salivation, lacrimation, piloerection, wheezing staining around mouth.

Body Weight: Not reported.

Necropsy: Not reported.

Classification: Core-Minimum Data, TOX Category III: CAUTION

Acute Dermal Toxicity

A 2 ml/kg solution was applied to the intact skin of two male + two female NZW rabbits and to the abraded skin of two male and two female rabbits on the fur clipped trunk for 24 hours under an impervious cuff. Observation was for 14 days.

Results: No deaths, LD50 > 2 ml/kg

Toxic Signs: A few white-colored lines along the abrasions were observed in a number of animals during the study period.

Body Weight: Not reported.

Necropsy: Not reported.

Classification: Core-Minimum Data, TOX Category III: CAUTION

3) C-33. An examination of Vantocil IB for potential carcinogenicity using two in vitro assays (Divisional ORG/42/78, CTL Ref: Y0156/001; Report No. CTL/P/492)

ICI study number: SV0034 - Salmonella reverse mutation test.

ICI study number: SV0035 - Mammalian cell transformation test.

(a) Salmonella Reverse Mutation Test

The Salmonella reverse mutation assay was conducted using the plate incorporation method as described by Ames et al (1975). The assay was conducted both with and without metabolic activation on two separate occasions. Five tester strains were employed (TA1535, TA1537, TA1538, TA100 and TA98). Where metabolic activation was utilized, a rat liver S9 mix derived from AROCLOR 1254 induced Sprague-Dawley rats was used. The incubation period was 72 hours. Positive controls used were 1,3-propane sulfone and N-2-flurorenyl-acetamide. Doses ranged from 4 - 2500 ug/plate. A positive response in the assay system was taken to be a two-fold or greater increase in the mean number of revertant colonies appearing in the test plates over and above the backround spontaneous reversion rate observed with the DMSO solvent, together with evidence of a dose-response.

Results: Positive controls gave positive mutagenic results and Vantocil IB gave negative mutagenic results with and without metabolic activation.

Conclusion: Vantocil IB is not mutagenic in the Salmonella test system

Classification: Core-Minimum Data

(b) The Mammalian Cell Transformation Test

The methods employed when testing a compound for potential carcinogenicity using growth of mammalian cells in semi-solid agar have been described in detail (Styles, 1977). A positive result is recorded when the transformation frequency per 10^6 survivors at the LD_{50} exceeds five times the control frequency. The cells used in this study were Baby Hamster kidney fibroblasts (BMK21/C13) which had a spontaneous transformation frequency of 35 per 10^6 survivors.

The solvent and negative control used in this experiment was DMSO, the positive controls used were benzidine (Expt 1) and acrylonitrile (Expt 2). All experiments were conducted in the presence of AROCLOR 1254 - induced rat liver S9 mix. Concentrations of test compounds in cell suspension ranged from 0.25 - 2500 ug/ml with benzidine as positive control, and 25 - 3000 ug/ml with acrylonitrile.

Results: No mutagenic activity was observed with Vantocil IB. Positive mutagenic results were obtained with benzidine and acrylonitrile.

Conclusion: Vantocil IB is not mutagenic in this test system.

Classification: Core-Minimum Data

4) C-36. Subacute Inhalation Toxicity (ORG/29/75; Report No. CTL/T/983)

Dynamic atomspheres of respirable particles of Vantocil IB were generated by a size-selective cyclone (Gage, 1968). The particles passed into a 'Perspex' acrylic resin exposure chamber of 60 liters capacity. The chamber and animal restraining tubes were so designed that only the snouts of the animals protruded into the atmosphere.

Groups of 4 male and 4 female rats (Alderley Park SPF albino strain) were exposed to the atmospheres for 6 hours per day, 5 days per week for 3 weeks. At the higher concentrations of Vantocil IB experiments were terminated earlier because of animal deaths. Between the exposure periods the animals had access to food and water ad libitum. They were weighed daily and their intake of food and water recorded. The animals were examined each day for evidence of gross toxicity with particular attention being given to any signs of nasal irritation and abnormal respiratory rate. After the last exposure 18 hour urine samples were collected and analysed for protein, glucose and bilirubin content, and the pH was determined.

Blood was taken for hematological examiantion and for biochemical estimation of urea, plasma sodium ion, potassium ion and ALT.

Animals were killed one day after the last exposure by prolonged inhalation of fluothane BP (Halothane) and the following tissues were taken for histopathological examination, lung, trachea, thymus, liver, kidneys, adrenals, spleen, heart, gonads, and epididymis and uterus. The tissues were processed by conventional methods and evaluated by light microscopy.

Results:

I. 26 mg/m^3 (respirable particles) of Vantocil IB.

Exposure of rats to this concentration resulted in very severe nasal irritation and marked dyspnea. They were exposed for 6 hours only and all animals died during the night following this exposure. Consequently no data were obtained for urine and blood analysis or from tissues for histopathological examination.

II. 12.5 mg/m^3 (respirable particles) of Vantocil IB.

Exposure of rats to this concentration also resulted in severe nasal irritation and dyspnea. During the first three days of exposure all animals lost weight and their intake of food and water was very low. One female rat died towards the end of the fourth exposure and the remainder died overnight. Consequently no data were obtained for urine and blood analysis or from tissues for histopathological examination.

III. 2.75 mg/m^3 (respirable particles) of Vantocil IB.

The rats that were exposed to this concentration presented similar evidence of nasal irritation and dyspnea, although less severe than that observed with 12.5 mg/m^3 (II above). Most of the animals in the test groups failed to gain body weight during the first three exposures.

Some slight increase was recorded over the weekend, however there was a dramatic weight loss in test animals after the fourth exposure.

Food and water intake after the fifth exposure was practically nil. One male died during the sixth exposure. Two males and one female died overnight. The remaining m ale and three females were killed with Fluothane BP. Blood samples taken for hematological examination revealed hemoconcentration and significant increases of methemoglobin in all animals.

Blood taken for biochemical analyses revealed no abnormalities. Histopathological examination of tissues revealed a moderate to severe pneumonitis in exposed animals. The reaction was patchy in character involving some alveoli and terminal bronchioles with more generalised macrophage activity throughout the whole of the alveolar bed. Small areas of epithelium desquamation were observed. Loss of cilia was also seen in certain areas of the thracheal epithelium.

The thymus glands from all Vantocil IB exposed animals showed severe depletion of lymphocytes and loss of normal architecture. There was a reduction in thickness of the cortex and a corresponding increase in reticular tissue. One female rat showed evidence of unilaternal pyelonephritis. Urine was not collected for biochemical analysis because of the condition of the animals.

IV. 0.25 mg/m^3 (respirable particles) of Vantocil IB.

Exposure of animals to this concentration resulted in moderate nasal irritation and tachypnea. The animals failed to gain normal body weight and three males and two females actually lost weight over the thirteen exposure periods (one male died after this exposure). The experiment was terminated after the thirteenth exposure. Food consumption in male test rats was low throughout.

Urine taken directly after the last exposure revealed no abnormalities apart from a low output of male test urine. The remaining animals were killed as before with Fluothane BP. Blood taken for hematological examination again revealed significant amounts of methemoglobin in all animals and hemoconcentration. Biochemical analysis of the blood revealed no abnormalities. Histopathological examination revealed slight to moderately-severe pneumonitis.

There was also evidence of accompanying resolution of the lung lesions in all the affected animals. The thymuses of 3 male and 3 female rats from the test group showed reduction in the cortical thickness and depletion of lymphocytes. Patchy loss of cilia in the tracheal epithelium was observed in three animals. The testis of one male showed degeneration of a few seminiferous tubules.

V. 0.025 mg/m^3 (respirable particles) of Vantocil IB.

Exposure to this concentration did not result in any signs of toxicity. Increases in body weight were erraric and low but intake of food and water was normal when compared with non-exposed control rats. No abnormalities were found in blood taken 18 hours after cessation of exposure. Urinalysis revealed no abnormalities. There was no evidence of either local or systemic chemical toxicity from histopathology.

Conclusion: No NOEL was established in this study. The LEL (lowest level tested) is 0.025 mg/m^3 and the effect was reduction in weight gain.

Classification: Supplementary Data

(a) Only 4 males and 4 females used per group.

TOX/HED:th:CFRICK:6-7-80

C. Frick
6/9/80